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RADIUM

EDITED BY
CHARLES H. VIOL, Ph. D.
AND
WILLIAM H. CAMERON, M. D.

VOL. X MARCH, 1918 No. 6

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A MONTHLY JOURNAL DEVOTED TO THE CHEMISTRY PHYSICS AND THERAPEUTICS OF RADIUM AND RADIO-ACTIVE SUBSTANCES

RADIUM

A MONTHLY JOURNAL DEVOTED TO THE CHEMISTRY, PHYSICS AND THERAPEUTICS OF RADIUM AND RADIO-ACTIVE SUBSTANCES.

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VOL. X MARCH, 1918 No. 6

METHODS OF PREPARING AND USING RADIOACTIVE SUBSTANCES IN THE TREATMENT OF MALIGNANT DISEASE, AND OF ESTIMATING SUITABLE DOSAGES.*

By William Duane, Ph., D., Boston.
(From the Cancer Commission of Harvard University.)

About four years ago the writer came to Boston, on the invitation of the chairman, and proposed to the Harvard Cancer Commission an investigation of the effects of radium rays on malignant disease, when applied by certain new methods. The Commission decided to take up the work, and we now see at the Huntington Hospital over five hundred new cases of malignant disease a year, almost all of which receive more or less treatment with radioactive substances. In some cases, very satisfactory results have been obtained, giving what may be called apparent cures. In others, marked alleviation has been observed, with prolongation of life and increased comfort; and in other cases still, no benefit, and possibly added discomfort, may have been produced. The fact that the medical profession keeps sending us so many cases for treatment would seem to indicate that we are doing a useful work in the community, and this, together with the character of the results actually obtained warrants the publication of a detailed statement of the methods employed in preparing the radioactive substances, of the methods of measuring the dosage, and of the general principles upon which the character of the treatment is determined.

* Reprinted from The Boston Medical and Surgical Journal; CLXXVII, 787-799, December 6, 1917.

The following paper contains a description of the scientific principles employed in the preparation of the applicators and of the instruments for measuring their radioactivity, and a brief statement of the kinds of cases in which the various methods are used and the dosages actually employed.

In order to make clear the principles underlying these investigations, it will not be out of place to state a few of the well-known facts and laws that have been discovered in the branch of science called "Radioactivity."

Radium is a chemical element belonging to the group of metals, but unlike most other elements, it is not extraordinarily stable. It transforms itself at a measurable rate into another substance called radium emanation. The rate of transformation, however, is so slow that about 1700 years would be required for half a given quantity of radium to disappear.

The emanation is a chemically inert gas, and it, too, transforms itself into a third substance called Radium A; but this is not all. Radium A transforms itself into Radium B, and Radium B into Radium C, etc., thus forming a series of substances related to each other as father to son. The last of the line known to exist is Radium F, also called polonium; which, as a matter of fact, was the first radioactive substance discovered by the Curies. Considerable evidence also has been collected of late years in favor of the supposition that polonium transforms itself into lead.

None of the above substances are gases except the emanation. Radium A, B, and C deposit themselves on anything and everything that comes in contact with the emanation, including the walls of the vessel that contain it. For this reason, Radium A, B, C, etc., frequently are grouped together under one name, and called collectively "deposited activity." These substances transform themselves much more rapidly than their grandparent, radium itself, does. Half a given quantity of emanation disappears in three and eighty-five-hundredths days; half a given quantity of Radium A, in three minutes; of Radium B, in twenty-six and eight-tenths minutes; of Radium C, nineteen and five-tenths minutes, etc. Thus the emanation lasts longer than the deposited activity; the former's life being measured in days, and the latter's in minutes. These substances differ from each other very much in their physical and chemical properties, but they have one characteristic in common,—they are radioactive.

By radioactive substance, we mean a substance that continuously emits peculiar types of invisible rays that differ substantially from light and heat rays. The radiation from radioactive substances, if sufficiently intense, destroys tissues, and this fact forms the basis of the therapeutic applications of the radioactive substances. In such applications, one or more of the radioactive substances, in a special container, is placed in or near the malignant growth to be treated, or is injected into the growth in the form of a solution, and the rays from the substance, passing through the tumor cells, destroy them.

Among the above-mentioned substances, Radium C produces by far the most penetrating rays. Radium B also emits some penetrating rays; but neither radium nor the emanation produces rays that are capable of passing through the walls of the glass tubes in which they are usually kept. "Why, then," it may be asked, "are tubes containing radium used for therapeutic treatment," The answer is that they are not so used until the radium has been in them long enough for the Radium B and C to

accumulate. When this has occurred, the only function fulfilled by the radium is to supply Radium B and C as fast as they destroy themselves, the latter being the real source of the penetrating radiation.

It follows, therefore, that, if by suitable means we deposit Radium B and C on an applicator or in a tube, we can use the applicator or tube to radiate tissues, just as if it contained radium itself, and this is the fundamental principle of the methods about to be described.

The deposit of Radium B and C can be obtained in a variety of ways, of which the following may be mentioned:

(1) The emanation may be extracted from the radium and pressed into a glass or metal container of any desired shape and size, and the Radium ABC allowed to accumulate in it. The container is then ready for use, either with or without the emanation, according to the length of time required for the treatment. The emanation, if left in the container, simply prolongs the time during which the activity lasts, by keeping up a supply of the Radium BC. The emanation itself does not add to the penetrating radiation.

(2) Radium ABC may be deposited on sheets of metal or other substances by leaving them for several hours in contact with the emanation contained in the closed chamber. The sheets are then attached to the tissues, to be radiated by adhesive plaster or otherwise.

(3) Radium ABC may be dissolved in water or other liquid, either by dissolving the purified emanation and allowing it to transform itself into Radium ABC, or by depositing the Radium ABC on grains of salt (or other substances) and then dissolving the salt in the liquid. In this way, a large amount of activity can be put into a few drops of liquid. The liquid is then injected in the tissues or blood-stream.

In order that these methods shall be of practical value, it is necessary to have an efficient machine for collecting and purifying the emanation. Such a machine was designed several years ago by the writer.

The general principles of the method are those previously employed by Ramsay and Soddy, Rutherford, and Debierne, in some of their most important researches. The advantages of the method described below are: that the purification does not require liquid air; that a large number of millicuries of emanation can be purified and compressed into a small fraction of a cubic millimeter, in ten or fifteen minutes of time; that no emanation is lost except that due to its natural decay; and that the process may be repeated a great many times without renewing parts of the apparatus.

Fig. 1 represents the arrangement of the glass tubes and reservoirs. The bulb A contains the radium salt dissolved in water. Radium in solution continually decomposes the water into hydrogen and oxygen, and at the same time transforms itself into the emanation, which is set free. The total volume of the hydrogen and oxygen amounts to more than two hundred thousand times that of the emanation at the same pressure and temperature. In addition to the oxygen and hydrogen and emanation, a small quantity of helium appears (the volume of which is a few per cent. greater than that of the emanation) and also traces of other gases, probably carbon dioxide and hydrocarbons coming from the decomposition of organic impurities, although the source of these traces of gas does not seem to be thoroughly understood. On account of its radioactive transformation, the exact proportion between the quantity of emanation and the gases with which it is mixed, depends upon the length of time the gases are allowed to accumulate. In the ordinary daily routine of our

laboratory, however, the problem resolves itself into the extraction of 140 to 240 millicuries of emanation having a volume of 0.084-0.144 cubic mm. at atmospheric pressure and ordinary temperature, from a mixture of gases, having a volume of 18 to 36 cc. at the same temperature and pressure.

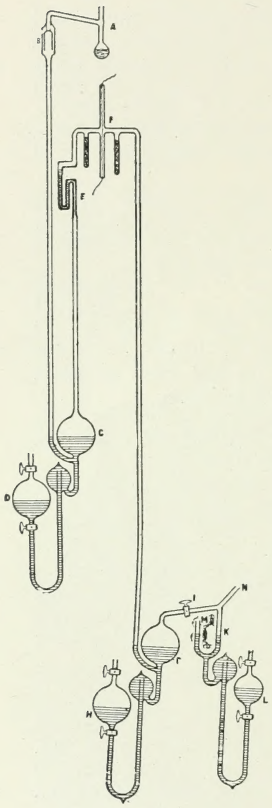

Fig. 1.

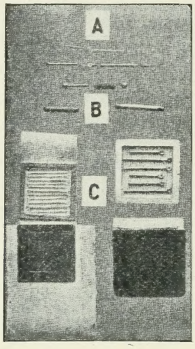

Fig. 2.

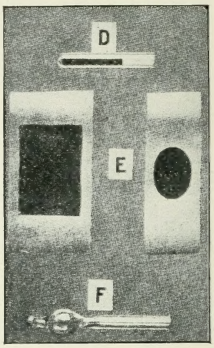

Fig. 3.

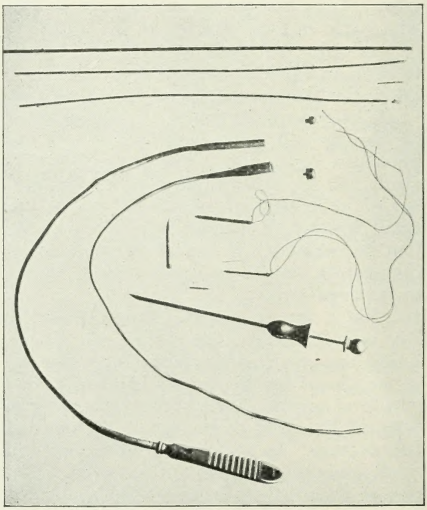

Fig. 4.

The mixture of gases collects in A and the tube B, and also, if the passage is open, in the reservoir C. Allowing the gases to collect in C apparently increases the efficiency, probably because the emanation

diffuses from the solution into a large volume more freely than into a small one. The tube B is considerably longer than 76 cm. so that air may be admitted into C, if desired, without its finding its way up into the radium solution. The trap at B protects against mercury spurting up into the radium solution, should some of the glass apparatus break. An ordinary water aspirator with suitable stopcocks controls the flow of mercury between the reservoirs C and D. On admitting the air into D, the mercury rises in C, pushing the mixture of gases through the mercury trap E, into the tubes F. The mercury in trap E holds back all but a very small quantity of the water vapor. The tubes F contain a copper wire, slightly oxidized, phosphorpentoxide and potassium hydroxide. although represented in the figure in a vertical position, the copper wire really lies horizontal. It is wound on a quartz rod supported by quartz feet, so that the wire does not touch the inner surface of the tube at any point. The diameter of the wire is 0·3 mm. and the length of the coil 25 cm. When heated red hot by an electric current of 5-10 amperes, it rapidly combines the oxygen and hydrogen, the phosphorpentoxide absorbing the water vapor formed. A small amount of copper oxide on the wire is required, because the mixture of gases contains (at least at first) a quantity of hydrogen that exceeds by a few per cent. the proportion required by the chemical formula for water. Some oxygen remains in the radium solution as hydrogen peroxide. The copper wire was heated for a long time to remove as much of the occluded gases as possible, and the phosphorpentoxide was distilled into its present position from a tube sealed on just below it, and afterwards removed, both of these processes taking place in vacuum. The potassium hydroxide is for the purpose of absorbing any carbon dioxide that may be present, or may be formed by the hot copper wire oxidizing hydrocarbon gases.

After the purification of the emanation the mercury in the reservoir G is drawn into H, the air being removed from H by the water aspirator, and the emanation and helium pass into G. The gases are then pushed up by the mercury through the stopcock I and into the desired tube or container, which is sealed on at N. The volume of the helium being very small, for the vast majority of purposes it is unnecessary to remove it. The length of the tube connecting E and G should be so great that air may be admitted into G without forcing the mercury up into F.

The stopcock I has a mercury seal, and contains no stopcock grease. A few marks made with a lead pencil on the stopper allow it to turn freely. It will be noticed that the emanation passes through no stopcock except the one at I, and even this is unnecessary, and has been added for convenience of manipulation only. The fact that stopcock grease and many other organic substances are decomposed by the rays from the emanation and give off gases is well known.

The system of tubes and bulbs K, L, M is for the purpose of removing the air from the other tubes and reservoirs, etc., by means of a pump attached at M. This must be done at the beginning, and after that no air enters the reservoirs except occasionally when it becomes necessary to renew the oxidized wire or the phosphorpentoxide, etc.

The apparatus in our laboratory has been in continuous use for more than four years. The bulb A now contains over nine hundred twenty miligrams of radium (element), and the total quantity of emanation purified per month amounts to more than 4.5 curies of emanation.

A curie is the quantity of emanation in equilibrium with one gram of radium (element).

One of the most important advantages in using the emanation instead of the radium salt itself for treating cancer, is that the emanation can be put into tubes that are very much smaller than the tubes would have to be to contain an equivalent amount of radium, and also because a much greater variety in the size and shape of the applicators can be obtained.

Figs. 2, 3, 4, and 5 represent some of the tubes and applicators in use in the Huntington Hospital. The small glass tubes at A in Fig 2 contain radium emanation. They were originally joined at N to the emanation apparatus represented in Fig. 1, and were sealed from it by means of a very small gas flame, after the emanation had been pushed into them by a column of mercury.

Usually these glass tubes are placed in steel tubes shown just below them in Fig. 2. The steel tubes have an eye that screws into one end, and a more or less sharp point that screws into the other end. The eyes are for threads, which are usually colored, and a record is kept of the amount of emanation in the tube. It often happens that for treating a particular case, it is desirable to cut off the easily absorbed rays, and this is done by surrounding the steel tubes by larger tubes (represented in Fig. 2), a millimeter or two thick, of silver or lead or platinum, according to the amount of filtration desired.

Sometimes it is desired to cover a large area of the skin with a lot of tubes of small strength. The metal frames in boxes represented at C in Fig. 2, are convenient for this purpose, and may contain either the glass tubes or the glass tubes inside the steel tubes; they are fastened by means of adhesive plaster as represented.

E (Fig. 3) represents the applicators on which the deposited activity has been placed. There is no emanation in them. In order to make these applicators, a sheet of metal is wrapped on the inside of a glass tube, as at D, and this glass tube is sealed on to the apparatus of Fig. 1, at N. The emanation is then pushed up over the mercury until it occupies the space inside of the metal sheet at D, and is left there for several hours for the deposited activity, Radium ABC, to accumulate. At the end of about three hours, the maximum amount has accumulated. The emanation is then withdrawn through the stopcock I in Fig. 1, into the globe G in order to save it, and after closing the stopcock the tube is cut off and the metal sheet spread out on adhesive plaster as at E in Fig. 3. The applicator is then applied over the area as desired. This method of treating cases is useful in very superficial lesions covering large areas, in which it is desired to get a uniform radiation over the whole surface. It has the advantage that a uniform, and, if desired, very small filtration can be obtained.

F in Fig. 2 represents a bulb used in preparing intensely radioactive solutions. A few grains of ordinary salt are placed in the small bulb at the extreme left end of the tube; the tube is then sealed to the emanation apparatus at N and the purified emanation, pushed up in between the grains of salt, and left there for three hours. The deposited activity, Radium ABC, accumulates on the grains of salt. At the end of three hours or so, the emanation is removed and put into the globe G; the glass bulb is cut off from the emanation machine, and distilled water squirted into the small bulb containing the activated salt. The salt dissolves in the water, carrying with it into solution most of the deposited

activity, Radium ABC. If care is taken to use the proper amounts of salt and distilled water, a physiological salt solution can thus be obtained, containing a very large quantity of deposited activity per cubic centimeter.

Solutions of this kind have been used in the Huntington Hospital for injections into the blood-stream and into tumor tissues.

Fig. 4 represents tubes that have been used in cases in which it was desired to insert the active substance into the tumor itself. This may be put in several ways; either the glass tubes may be put into the tumor through a trochar and left there, or they may be placed inside of metal tubes such as represented in the figure, made long or short, thick or thin, then withdrawn after the desired period of time has elapsed. If the glass tubes are put into the tumor through a trochar and left there, a very prolonged radiation ensues. The emanation disappears, little by little, half of it decaying in slightly less than four days, half of what is left in four more days, etc., so that the tissues are radiated for several weeks continuously, though with progressively decreasing intensity. In certain types of tumors this is by far the most effective method of using radium that I have tried.

Long metal tubes, such as those represented at the right side of Fig. 4, have been used for inserting the radioactive substance into tumors that lie some distance below the skin. A little glass tube containing the emanation lies in the end of the metal tube, close to the sharp point. The two curved instruments in Fig. 4 are of silver and have been used in cases where some filtration was desired. In the thicker one, the hole containing the glass tube has been bored eccentrically, thus giving a much greater filtration on one side than on the other.

Fig. 5 represents the tubes and applicators that are used for intrauterine conditions, and in cancer of the cervix. The figure also shows the applicators employed in cases where it is desired to hold the radioactive substance at some distance from the skin, as in leukemia and malignant lymphomata.

The small metal cones are used with the steel tubes, to raise them above the surface of the skin, and thus produce uniform radiation over certain areas. These cones hold the steel tubes at distances of 1 cm. to 2 cm. from the surface of the skin. There are various sizes to correspond to the areas of superficial lesions.

The large lead applicator on the brass support is used to give a "distance filtration," of six centimeters or so.

The gauze wrapped around some of the lead applicators serves two purposes; firstly, it cuts off the secondary radiation coming from the surface of the lead, which is not very penetrating, and would produce considerable irritation in the skin; and, secondly, it raises the applicator up from the surface of the skin, thus, according to the inverse square law, reducing the amount of radiation absorbed in the skin as compared with the amount absorbed at a considerable distance below the surface.

It is of the greatest importance in treating malignant disease to be able to vary the penetration of the rays at will, and at the same time to know accurately how penetrating the rays are. The applicators described above provide a very flexible technic with penetration of rays varying within wide limits.

The absorption of rays from radioactive substances by tissues appears to be a very complex phenomenon, and a special article on this subject is in preparation.

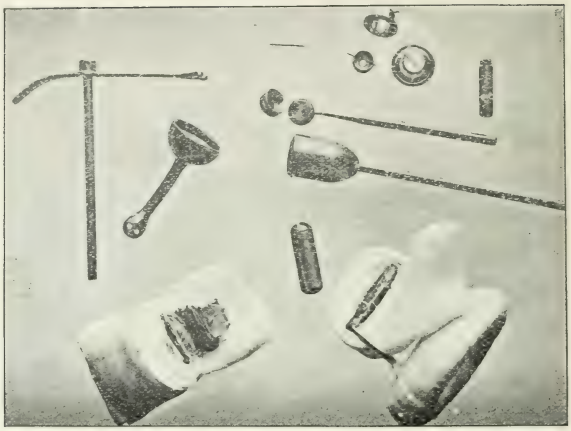

Fig. 5.

Whenever Nature acts, she acts quantitatively as well as qualitatively. Physics deals almost exclusively with quantitative measurements. The importance of estimating phenomena quantitatively, of making exact dosages, is nowhere greater than in the application of the radioactive substances in the treatment of cancer. One must send through the tissues, not simply radiation, but enough radiation to destroy the tumor, and one must be sure to use radiation sufficiently penetrating to reach all the diseased tissues.

The first step in a quantitative estimate of dosage is to measure the quantity of radium, of emanation, or deposited activity, as the case may be, that the applicator contains.

The following paragraphs will be devoted to a description of our measuring instruments. There are three of them:

(*a*) An instrument for accurately measuring the quantity of the radioactive substance in the applicator, or in a piece of tissue, as the case may be. This instrument is in our laboratory in a room at a considerable distance from the emanation apparatus. The emanation gradually diffuses through the halls and rooms, and leaves behind it on the walls, floor, furniture, etc., the deposited activity, which in time will make delicate and accurate measurements of radioactivity impossible in the part of the building near the emanation apparatus.

(*b*) An instrument for roughly and rapidly estimating the quantity of radioactive substances in tubes and applicators. This instrument is in the hospital in the room in which most of the radium treatments are given, and is used frequently to make sure that the tubes and applicators are in order.

(*c*) An instrument for detecting the presence of radioactive substances. This instrument is a simple form of electroscope, and is used for finding lost tubes that have been thrown away with the bandages, ets., and for ascertaining whether or not the small glass tube previously inserted into the tumor is still intact, and has not been broken.

Fig. 6 represents the apparatus used for accurately measuring the

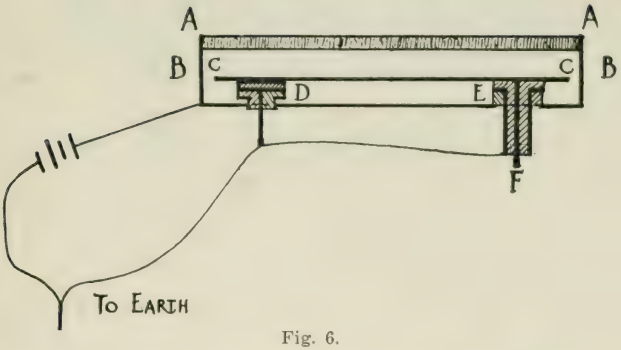

Fig. 6.

quantity of the radioactive substance in the applicator or tissue. AA is a sheet of lead 50 cm. in diameter and 1.5 cm. thick. It rests on top of a circular brass box, BB, the same diameter as AA, and about 3 cm. deep. A horizontal brass disk, CC, lies in the center of this box, and is insulated from it by hard rubber supports, DE. The box B is charged by joining it to one pole of a battery having an electromotive force of 100 volts or so, and in order to prevent the current from passing from the box B to the disk C through or along the surface of the supports DE, the supports are supplied with metal disks and rods joined to earth as represented. Thus any current starting from the box B along the surface of D would meet this conductor, and pass off to earth without reaching CC.

In order to measure the quantity of a radioactive substance in an applicator, the applicator is placed on top of the lead disk AA. The penetrating gamma rays from this substance then pass through the disk and into the box, where they make the air in the box a conductor of electricity. Under ordinary conditions, air is not a conductor of electricity, but the radium rays have the power of making the air a conductor of electricity, and this phenomenon is called the ionization of the air. When the air is ionized, the current passes across from the box B to the disk C. The greater the amount of the active substance on top of the lead AA, the greater will be the amount of radiation passing through the air in the box, and the greater will be the current flowing from the box to C. This current, under proper conditions, is proportional to the quantity of the radioactive substance on the lead, and is universally regarded as the most satisfactory measure of that quantity.

In order to measure the current flowing from the box to C, one of the supports, E, is perforated, and a wire, F, passes through it and is connected to an instrument for measuring currents of electricity.

The most satisfactory method we have found for measuring the current is to use a variable electrical condenser and quadrant electrometer. A very convenient variable condenser for the purpose has been designed by Dr. Harry Clark, who has charge of the laboratory experiments in our course in Radioactivity.* Fig. 7 represents the apparatus. A pile of fixed plates, A, insulated from the rest of the apparatus, is joined to one quadrant D of an electrometer, and also to the wire F in Fig. 6, through which the current from CC comes. Two movable

* Physical Review, July, 1915, pp. 43-45.

piles of semi-circular plates, B and C, insulated from each other, are mounted on the same support in such a way that they rotate about the

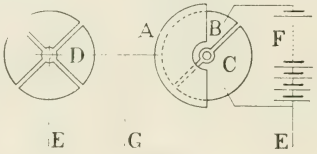

Fig. 7.

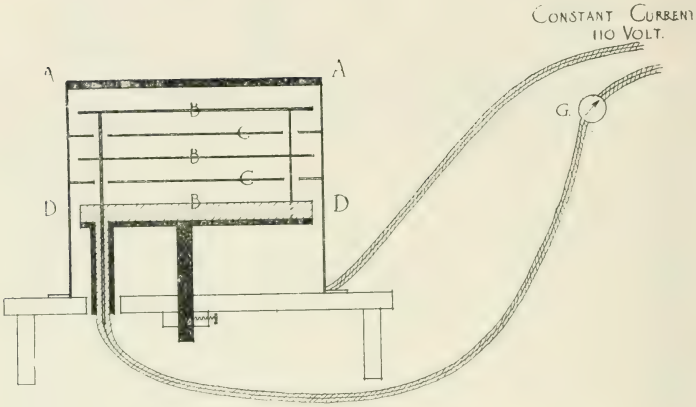

Fig. 8.

axis, and slide in between plates A without touching them. One set of plates, B, is joined to a battery of constant electromotive force, while the other set is put to earth. Under these circumstances, a rotation of B and C in one direction or the other will cause a charge of electricity to be induced on the plates A; if B and C are rotated at just the right rate, this charge will exactly neutralize the current coming to G from the box of Fig. 6. The rate at which B and C must be turned in order that this neutralization shall take place can be determined by observing the quadrant electrometer D. The plates must be turned just fast enough to keep the electrometer needle at rest. Under these conditions, if the plates at B and C are always turned through the same angle (and stops in the instrument are so placed that this is the case), then the current is inversely proportional to the time required to turn the plates through the angle, and this time is therefore the measure of the current coming from the ionization chamber. In this method, the quadrant electrometer acts simply as an instrument for detecting small charges of electricity.

In order to measure quantities of the radioactive substances in terms of standard units, the apparatus must be standardized. This is done by placing on the lead plate AA of Fig. 6 a sealed glass tube con-

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taining a known quantity of radium, and by measuring the ionization current that this produces.

The unit in which quantities of emanation are expressed has by international agreement been defined to be the quantity of emanation that is in equilibrium with one gram of radium element. For practical purposes, this quantity of emanation in a small sealed tube would produce the same penetrating radiation as a gram of radium, for it would have associated with it practically the same quantity of Radium B and C. Consequently, the number of millicuries of emanation in the container, divided by the number of milligrams of radium in the standard, is equal to the ratio of the measured currents when the emanation tube and the radium tube are placed on the lead disk AA, respectively, and these currents are inversely proportional to the two measured times. Hence, practically all that is necessary to do in measuring the quantity of emanation is to divide a certain constant by the measured time.

Fig. 8 represents the instrument in the hospital, used for roughly estimating the strength of the tubes and applicators. AA is a lead disk 30 cms. in diameter and 1 cm. thick, upon which the tube or applicator is placed. BB, etc., are thin sheets of aluminum, supported by metal rods and joined through an insulated copper wire to the galvanometer G. CC are plates parallel to BB, but fastened to the metal box DD, which in turn is joined by an insulated wire to one pole of a battery, or one terminal of an electric light current furnishing constant current at 110 volts, the other terminal being joined to the galvanometer as represented.

When the applicator containing the radioactive substance is placed on AA, the penetrating rays from it pass through the lead disk AA into the box DD, where they ionize the air. The current then passes from the box through the plates CC, across the air space to the plates BB, and then through the supports and wire circuit to the galvanometer, and thence back to the source of current. The galvanometer deflection is most conveniently read by means of a mirror, lamp and transparent scale. The deflection of the spot of light on the scale measures the current and thus the quantity of activity in the applicator, provided that the deflection of the galvanometer produced by a known quantity of radium has first been obtained.

This instrument is not quite as accurate as the one described above, but is much more convenient and the measurement can be made much more rapidly, for all that is necessary to observe is simply the deflection of the spot of light on the scale.

In order to illustrate the effects produced by the rays on cancer tissue, and, especially, to give an idea of the quantity of the radioactive substance, the time and the filtration required to produce given effects with the above-described methods of treatment, the following cases are cited, chosen from the records of the Huntington Hospital. The history and diagnosis of the disease, and the clinical findings, will be discussed in other sections of the report, by various members of the hospital staff.

The following cases represent treatments of epidermoid carcinoma. This group of cases is by far the largest of any that we have treated. In selecting illustrations, the most extensive lesions that we have been able to influence favorably have been chosen, so that an idea may be obtained as to the limits of what can be done with the amount of radium at our disposal, namely, 230 milligrams of the element. (Since the period cov-

Case 1. a—June 7, 1915.

Case 1. b—Jan. 12, 1916.

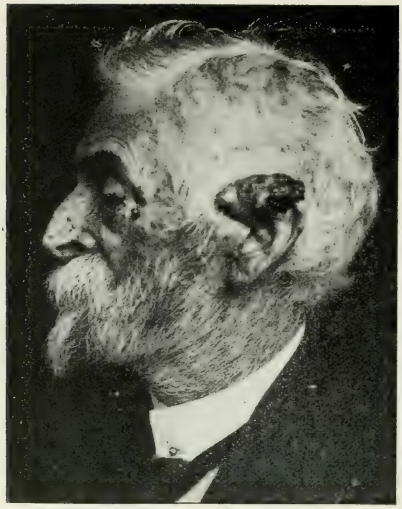
ered by this report, our supply of radium has been increased to about 1 gram.)

Case 1 represents a recurrence after operation. The pathological diagnosis was epidermoid carcinoma. The treatment given consisted almost entirely of the insertion of small glass tubes containing a few (from 1 to 9) millicuries of radium emanation. The glass tubes remained in place for ten days or two weeks at a time. The treatment began on May 27, 1915, and lasted for nearly a year, at greater or less intervals of time. A practically continuous stream of radiation passed through the tumor for the first six weeks. Two recurrences took place. The figures illustrate the condition of the lesion near the beginning of treatment, on June 7, 1915, and on Jan. 12, 1916. The second recurrence took place after this date, the disease having progressed through into the mucous membrane of the right cheek.

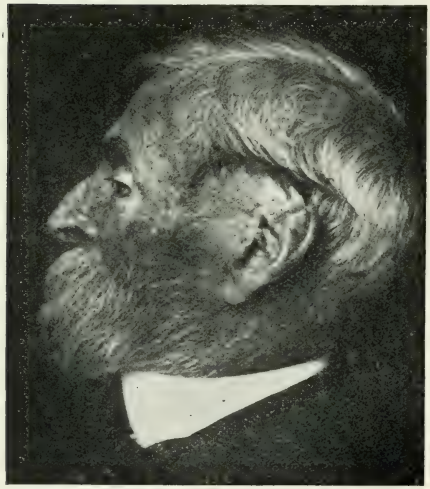
Case 2 represents a condition the pathological diagnosis of which was also epidermoid carcinoma. This lesion was treated almost entirely by the insertion of glass tubes through a trochar into the tissues, giving a prolonged treatment. Treatment began on October 14, 1915, and lasted until May 26, 1916, at intervals varying from one week to two months. The glass tubes contained amounts of emanation varying from 2 to 10 millicuries, and the tubes remained in place on an average of about two weeks. During the latter part of the treatment, the tumor tissue had practically disappeared, and during this period a few treatments were given with steel tubes, each containing from 15 to 34 millicuries, the treatment lasting from one-half to one and one-half hours. The photographs represent the condition of the lesions before and after treatment.

Case 2. a—Oct. 27, 1915.

Case 2. b—July 21, 1916.

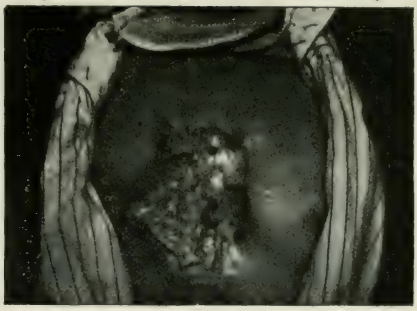


Case 3. a—July 7, 1915.



Case 3. b—Nov. 17, 1916.

Nov. 2, 1913.



May 28, 1914.

CASE 5—PATHOLOGICAL DIAGNOSIS: SARCOMA.

Two fragments were removed from the scar on July 14, 1916, for pathological examination, and Dr. Tyzzer reported that one fragment consisted of necrotic tissue and hyalinized blood clot. The other fragment consisted of an abnormal connective tissue, covered with thick squamous epithelium. Pathological diagnosis: no evidence of new growth.

The condition of these lesions had not perceptibly changed when the patient died of pneumonia on January 24, 1917.

Case 3 represents a series of keratoses widely distributed, some of which, according to pathological report, had definitely degenerated into epidermoid carcinomata. The large tumor growing on the left ear was treated by the prolonged radiation method, the small glass tubes containing a few millicuries of emanation being left in the tissue for two to three weeks. The other lesions were treated by means of the steel tubes with filtration of a few millimeters of air and cotton. The usual length of the steel tube treatment was from one-half to one and one-half hours, and the amount of emanation in the tubes varied from 14 to 47 millicuries. Treatment began on July 7, 1915, and lasted, at intervals of from one week to two months, until January 2, 1916.

The photographs represent the condition of the lesions on the left hand side of the face before and after treatment. The last treatment of the tumor on the left ear was given on August, 24, 1915. During the interval from July 7 to August 24, eight glass tubes containing a total of 50 6-10 millicuries of emanation were inserted into this tumor, and left in place. Four steel tubes were also used during this period, each for about one hour, containing from 15 to 35 millicuries of emanation. On July 14, 1916, a specimen was removed from the scar on this ear, for pathological diagnosis. Dr. Tyzzer reported that the specimen consisted of cartilage, in part necrotic, against which lay a layer of fibrino-purulent exudate. Superimposed was a layer of dense, degenerative connective tissue, and at the surface, fibrino-purulent exudate. Pathological diagnosis: no evidence of tumor.

The condition of the lesions in March, 1917, when the patient was last seen at the hospital, did not differ perceptibly from that represented in the photograph of November 27, 1916.

Nov. 2, 1913.

May 28, 1914.

CASE 5—PATHOLOGICAL DIAGNOSIS: SARCOMA.

The three cases cited above illustrate what may be termed the prolonged radiation treatment. There are, in general, three important factors entering in a quantitative way into the effects produced by the radiation: (*a*) the amount and distribution of the radioactive substance used, (*b*) the time of exposure to the rays, and (*c*) the filtration. The question as to the effects produced by a small quantity used for a long time, as opposed to a large quantity used for a short time, has not been definitely decided for all cases. In the above treatments, the time element was very large, for the tumors were subjected to continuous radiation for six weeks or two months at a time, the intensity of the radiation being correspondingly small. Thus the time element was enormously increased at the expense of the intensity element. The method has another great advantage also, in that the most energetic of the radioactive rays are used to their fullest extent. The walls of the glass tube being very thin, they absorb very little radiation, which means that a very large percentage of the radiant energy is absorbed in the tissues within a few millimeters of the tube. The distance to which the radiation extends depends to a considerable extent upon the thickness of the glass. In general, the tubes are such that the destructive action on normal tissues caused by the rays, extends to a distance of 7 or 8 millimeters. Under these conditions, epidermoid carcinoma tissue will be destroyed at a considerably greater distance. If it is desired to extend still further the limits of the destructive action, larger doses must be used.

Case 6—Jan. 9, 1916.

April 1, 1917.

PATHOLOGICAL DIAGNOSIS: MALIGNANT LYMPHOMA (HODGKIN'S DISEASE.)

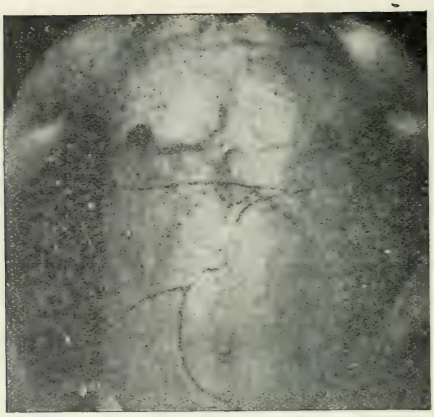
In spite of the fact that the radiation of the tumor lasted continuously for six or eight weeks, no destructive effect was produced on neighboring healthy tissue. A slight erythema, however, appeared for a distance of 2 cms. or so around the lesions.

Cases 2 and 3 above represent the most extensive epidermoid carcinomata that we have been able to destroy so completely that the presence of the carcinoma tissue could not be demonstrated. We have treated a large number of similar cases, and cases of less extensive lesions, which it is unnecessary to describe in detail.

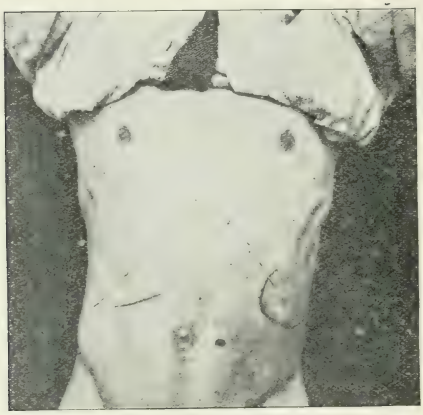
The method of inserting glass tubes through a trochar can be applied only to cases in which the lesion occupies a certain volume. Conditions in which the epidermoid carcinoma tissue is distributed in a more or less thin layer, over a large or small area, must be treated in other ways.

Case 4 represents one of the most extensive lesions of superficial carcinoma that we have treated at the hospital. It illustrates the limit of what we have been able to do with the radium at our disposal. A large number of smaller lesions have been completely removed by the radium treatment. This case demonstrates the effects that can be obtained by a very large number of separate treatments, extending over long periods of time. Radium applications began on February 2, 1914, and the patient is still under treatment. The disease has never disappeared entirely, but the treatment has kept it under control, so that the carcinoma tissue has not extended superficially, and no physical evidence exists that internal metastasis has ocurred. During the three years and more that have elapsed since the beginning, the patient has received 64 treatments, with quantities of emanation ranging from a few millicuries up to 142 millicuries. The length of each treatment varied from 1 to 3 hours, and the filtration varied from that due to the glass walls of the emanation tubes themselves, to two millimeters of lead, depending upon the area and thickness of the portions of the tissue to be treated. There has been a marked general improvement in the condition of this lesion, an improvement that has been maintained.

The following sarcoma case illustrates the effects that can be obtained by inserting metal tubes containing radium emanation into the center of the tumor tissue itself. It was one of the earliest cases treated



June 4, 1914.



March 20, 1914.

CASE 7—PATHOLOGICAL DIAGNOSIS: MYELOGENOUS LEUKEMIA.

at the hospital, and the satisfactory results obtained are largely due to Dr. Ordway's skill in making the applications. The patient has remained free from signs of recurrence to the present date.

The record contains a number of pathological reports, which give sarcoma with numerous mitotic figures as the diagnosis. The radium applications began on November 28, 1913, and lasted until August 6, 1914. During this period 22 radium treatments were given, the maximum dose recorded being 59 millicuries. The treatments consisted of two kinds: in one the metal tubes were inserted with very small filtration into the tumor tissue itself; in the other, the tubes were laid on the surface, with filtration varying in amount from a fraction of a millimeter of steel,

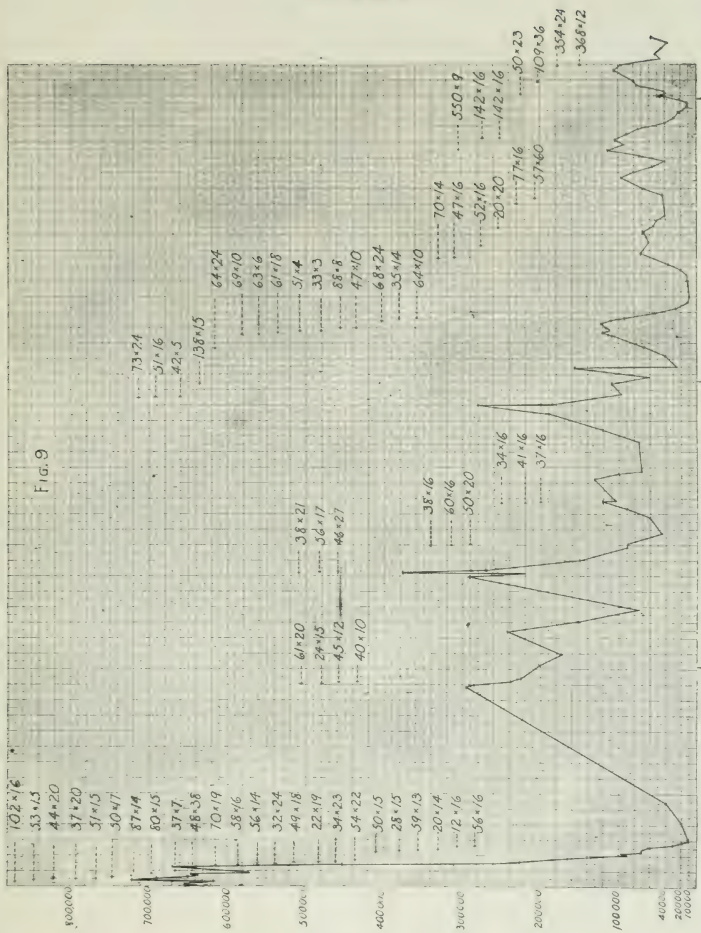


Fig. 9.

to one millimeter of lead. The length of time varied from one to twenty-four hours. It is probable that the favorable results obtained in this case are due to prolonged treatments, in which the tubes were inserted into the tumor itself.

It is a well-known fact that the large masses of tissue that occur in malignant lymphomata (Hodgkin's disease, lymphosarcoma, etc.) are peculiarly susceptible to radiation. These masses disappear under the action of the rays, but they are very apt to recur; if not in the same place, at other points in the body, and the radiation of one mass has no destructive effect upon masses at a distance. The following case is cited

as illustrating the destructive effect that can be produced on this type of tissue by prolonged exposure to the rays from a relatively small amount of radium.

Case 6 represents, perhaps, the largest masses of tissue that we have been able to cause to disappear. The tumor has been subjected to radiation a large number of times between January, 1916, and April, 1917. The doses varied from 31 to 550 millicuries, and the time of exposure from 8 to 48 hours. The total number of millicurie hours during the entire treatment amounted to 93,756. This case is still under treatment.

The method of treating these cases differs fundamentally from that employed in those previously mentioned. Only the penetrating gamma radiation is allowed to pass through the tissues, the filtration being two millimeters of lead, and about two to three cms. of gauze; sometimes, also, the applicator is held on a brass frame at a distance of 6 or 7 cms. from the skin, in order to reduce the skin effect in proportion to the radiation of the underlying tissues. The gamma radiation that goes through this amount of matter carries with it an exceedingly small quantity of energy, and it is one of the most extraordinary facts connected with these mysterious substances that such a small quantity of energy can have any appreciable effect on such large masses of living tissues.

As is well known, x-rays produce marked alleviation in cases of myelogenous leukemia, and the fact that radium also has much the same effect was observed in Paris years ago. The best method of treating leukemia with radium is substantially that described above in the case of malignant lymphomata. The emanation tubes, in a lead box with walls about two millimeters thick, are placed at different positions over the spleen, and left there from four to six hours, when they are changed to other positions. The chart in Fig. 9 represents the effect of the radiation on the white cell count of the blood, the figures giving the dosage. The first figure represents the number of millicuries, and the second the number of hours of treatment, respectively. It will be noticed that every series of treatments is followed by a diminution in the white count, even though this is given after a large number of recurrences.

The fact that there is a general decline in the magnitude of the recurrences during the three years in which the patient received treatment is the most hopeful characteristic to be noticed. Attention is called to the fact, however, that larger doses have been used the last few months than before. This chart refers to Case 7, and photographs representing it are also given. These photographs show the diminution produced in the size of the spleen during the first part of the radiation. The spleen has remained small ever since.

Here, again, the size of the effect produced by a small amount of radiated energy is noteworthy. It would take rather delicate chemical tests to discover the chemical change produced by this radiation in so large a quantity of matter.

An exceedingly interesting study of a large number of cases of leukemia treated with radium will be published by Dr. Peabody in a special article on the subject.

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